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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/628,792	07/28/2003	Jon A. Wolff	Mirus.040.01	5528

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EXAMINER	
HA, JULIE	
ART UNIT	PAPER NUMBER
1654	
MAIL DATE	DELIVERY MODE
11/25/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/628,792	WOLFF ET AL.	
	Examiner	Art Unit	
	JULIE HA	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 August 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4,6-8 and 12-30* is/are pending in the application.

4a) Of the above claim(s) *28* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4,6-8,12-27,29 and 30* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on August 27, 2008 has been entered. Claims 3, 5, 9-11 have been cancelled. Claims 1-2, 4, 6-8, 12-30 are pending in this application. Claim 28 remains withdrawn from further consideration, as being drawn to nonelected species. Claims 1-2, 4, 6-8, 12-27 and 29-30 are examined on the merits in this office action.

Claim Identifier

2. Applicant filed 4 pages of claims on August 27, 2008. Pages 2-3 indicate claims 3, 5, 9-11 are cancelled and claim 28 is withdrawn. Pages 4-5 indicate that claim 5 is cancelled. However, pages 4-5 are missing claim identifiers for claims 3, 9-11 and 28 (claims 3, 9-11 and 28 are entirely missing from the claim set). Examiner examined claims 1-2, 4, 6-8, 12-27 and 29-30 according to pages 2-3 of the claims. Applicant is required to delete claim pages 4-5, since they are duplicates of pages 2-3, missing correct claim identifiers.

Withdrawn Rejection

3. Provisional Obviousness Double Patenting Rejection of claims 1-2, 4, 6-8, 12-17, 29-30 being unpatentable over claims 1-18 of co-pending Application No. 09/000,533 in view of Rozenberg et al (US 2002/0064520) is hereby withdrawn in view of Applicant's arguments.

Maintained Rejection

35 U.S.C. 102

4. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

5. Claims 1-2, 4, 6-8, 12-27 and 29 are rejected under 35 U.S.C. 102(b) as being anticipated by Twist et al (US Patent # 5633230).

6. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue.

7. Twist et al teach the assessment of peptide distribution, in vivo. The distribution and localization of a ^{14}C-acetyl form of peptide AV9 was determined following administration by intravenous and sub-cutaneous injection dissolved in 10 ml PBS. The reference teaches that both i.v. and s.c. injection brought about rapid distribution of drug to tissues. The highest and most prolonged levels are attained in the liver, followed by

the kidneys and spleen (see Example 4). Since the active steps of the process are disclosed in Twist patent '230, and the subsequent claims do not alter the active step of the process, Twist reference meets the limitations of claims 1-2, 4, 6-8, 12-27 and 29.

Response to Applicant's Arguments

8. Applicant argues that "the claims recite that it is the volume and rate of injection that causes increased vascular permeability. As shown by the 1.132 Declaration filed 4/21/2008, Twist et al do not inject a volume sufficient to cause vascular permeability. Therefore, Twist et al do not teach all the limitations of the Applicant's claim." Applicant further argues that "the solution used by Twist et al is not hypertonic. With respect to the injection solution of Twist et al causing increased vessel permeability, Applicant can find no teachings in 5,633,230, for either a hypertonic injection solution or a desire for or observation of increased vessel permeability, increased extravascular fluid volume within the target tissue, or swelling of the target tissue."

9. Applicant's arguments have been fully considered but have not been found persuasive. Twist et al teach the administration of protein or peptide to the target tissues (liver, kidneys and spleen). The active steps of the process are disclosed in the Twist reference, and the subsequent claims do not alter the active steps of the process. The only active step recited in the base claim is "inserting an injection solution containing protein or peptide into the lumen of an efferent or afferent vessel of the target tissue." The instant claims do not recite the volume injected, or the pressure applied. Therefore, the amount of injection administered in the Twist reference would cause a transient

increased vascular permeability in the target tissue, since the injection solution taught in the Twist reference is hypertonic. Hypertonic injection solutions would inherently increase the permeability. In the declaration under 37 C.F.R. 1.132, Applicant argues that the "injection volume of 400 μL injected by Twist reference into the tail vein of a mouse resulted in no measurable increase in intravascular pressure in the Inferior Vena Cava near the junction of the hepatic vein." Further, "injection of 400 ml, followed by a second injection of 400 μl, also showed no significant increase in intravascular pressure." However, it would be inherent when an injection volume is increased to 2.5 ml (as in the graph), the pressure in the Inferior Vena Cava near the junction of the hepatic vein or other extravascular cells would increase due to the increased volume of the injection. Furthermore, the increased volume (e.g., from 400 μl to 2.5 ml) would also inherently increase the vascular permeability in the target tissue. In regards to column 8, line 16 of patent '230, the reference teaches that the compounds are formulated for administration by infusion, or by injection either subcutaneously or intravenously...in saline, phosphate-buffered saline or 5% dextrose solution (see column 8, lines 6-18). The PBS (pH 7.02) was prepared by combining 400 mL of 8 g/L sodium phosphate monobasic (dehydrate), 600 mL of 9.47 g/l sodium phosphate dibasic (anhydrous), and 4.61 g NaCl in a 1 L volumetric flask (see column 10, lines 2-7). 1X PBS would have different salt concentrations (for example, 137 mM NaCl, 10 mM phosphate, 2,7 mM KCl), therefore, this would be a hypertonic solution. Since the instant claims 25-26 recite the injection solution contains less than 20 mM salt and less than 5 mM salt, and PBS has different salt concentrations, this would meet the limitation of hypertonic solution,

and injection solution having less than 20 mM and 5 mM salt concentration. Therefore, Twist et al anticipates the claimed invention.

10. Claims 1-2, 4, 6-8, 12-27, 29 and 30 are rejected under 35 U.S.C. 102(b) as being anticipated by Goddard et al (US Patent # 5602094).

11. The instant claims are drawn to a process for delivering a molecule, and the active steps of the process is inserting an injection solution containing the molecule into the lumen of an efferent or afferent vessel of the target tissue. Claim 30 recites the rapid insertion of a sufficient volume of injection solution.

12. Goddard et al teach the treatment of tumors by administration of PLAP peptide. The reference teaches that two groups of 12 rats were injected with the PLAP and with agarose beads alone (as control). In order to ensure uniform distribution of the bound peptide, the total volumes were increased to 10 ml by the addition of 6 ml sterile saline solution immediately prior to injection. The reference teaches that 72 hours after injection, the rats were euthanized and tumor effusions were aspirated (see column 4, lines 25-45). Since the active steps of the process are disclosed in Goddard patent '094, and the subsequent claims do not alter the active step of the process, Goddard reference meets the limitations of claims 1-2, 4, 6-8, 12-17 and 29-30.

Response to Applicant's Arguments

13. Applicant argues that "'inserting an injection solution containing the protein or peptide into the lumen of an efferent or afferent vessel of the target tissue' is actively

qualified in that the injection volume and rate must 'cause transient increased vascular permeability in the target tissue, increased extravascular fluid volume within the target tissue, and swelling of the target tissue'".

14. Applicant's arguments have been fully considered but have not been found persuasive because Goddard reference teaches the active step recited in the instant claims. The instant base claim 1 recites the active step "inserting an injection solution containing the proteins or peptide into the lumen of an efferent or afferent vessel of the target tissue." Goddard reference teaches the injection of PLAP protein into the target tissue (tumor). Since a large volume (10 ml) is injected into the target tissue, it would inherently cause an increased vascular permeability, swelling of the target tissue, and increasing the pressure at the target tissue junction. The instant claims do not recite the volume amount or the rate of injection. Since the active method steps are met by the Goddard reference, the reference anticipates the instant claims.

Obviousness Double Patenting

15. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

16. A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.
17. Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

18. Claims 1-2, 4, 6-8, 12-27 and 29-30 are rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1-12, and 14 of U.S. Patent No. 7,144,869 in view of Rozenberg et al (US 2002/0064520). Although the conflicting claims are not identical, they are not patentably distinct from each other because if one practiced the claimed invention of the instant application, one would necessarily achieve the claimed invention of U.S. Patent '869.

19. The instant claims are drawn to a process for delivering a molecule to an extravascular cell in a mammalian target tissue (liver cell, hepatocyte) in vivo and blood vessel consists of a vein.

20. The claims of U.S. Patent '869 are drawn to a process for delivering a polynucleotide to a primate liver cell, comprising a) transiently occluding afferent and efferent blood vessels of the liver in a primate; and b) injecting the polynucleotide in a solution into the lumen of a hepatic Bessel wherein the injection of the solution results in portal vein pressure of 10 mm Hg or greater (see claims 1-11). Claim 7 recites that the polynucleotide consists of naked DNA (not associated with a transfection reagent or other delivery vehicle). Claims 12 and 14 are further drawn to the hepatic vessel consists of hepatic vein and portal vein. Assuming about 330 daltons per nucleotide, this implies that for a pair of nucleotide, the molecular weight is 660 daltons. The

molecular weight of the DNA would depend on the size of the DNA. The difference between the reference and the instant claims is that the reference does not teach the delivery of protein or peptide to the target tissue.

21. However, Rozenberg et al teach vectors for cell-specific gene delivery to a target cell, and the vectors comprise a recombinant core containing the genetic materials to be delivered (see abstract). The reference further teaches a non-naturally occurring gene therapy vector for cell-specific delivery of nucleic acid to a target cell, wherein at least one expression product of said vector is a therapeutic nucleic acid, peptide or protein (see claim 1). The reference further teaches the method of treating a disease in a patient, comprising administering to said patient a therapeutically effective amount of a vector according to claim 1 (see claim 8).

22. Therefore, it would have been obvious for one of ordinary skill in the art to deliver the protein or peptide directly to the target tissue, since patent '869 teaches the delivery of DNA or RNA into the target tissue, and Rozenberg et al teach the delivery of vectors expressing nucleic acid encoding proteins or peptide to the target tissue of the patient. One of ordinary skill in the art would be motivated to combine the teachings, since the teachings show that both DNA or RNA or nucleic acid encoding the proteins or peptides can be delivered to the target tissue. There is a reasonable expectation of success, since DNA or RNA or nucleic acid encoding the protein or peptide can be delivered to the target tissue, so one would expect that the proteins or peptides would also be delivered to the target tissue.

Response to Applicant's Arguments

23. Applicant argues that "US 2002/0064520 teaches modification of viral nucleocapsids through attachment of immunoprotective elements, targeting elements, and/or cell-entry elements...further teaches at paragraph 0069 that their vectors are administered in vivo by methods that are well known in the art. However, US 2002/0064520 fails to show any in vivo delivery, showing only in vitro delivery of their vectors to cells. Therefore, the teachings of US 2002/0064520 expresses only the desire to deliver their vector in vivo and no mechanism by which there vectors can be delivered to extravascular cells in vivo." Applicant further argues that "7,144,869 was filed after the publication of US 2002/0064520 teaches only delivery of naked nucleic acid. Thus, prior to Applicants' invention, a method to deliver proteins or peptides to extravascular cells in vivo was not known."

24. Applicant's arguments have been fully considered but have not been found persuasive. Rozenberg reference claims a non-naturally occurring gene therapy vector for cell-specific delivery of nucleic acid to a target cell…wherein at least one expression product of said vector is a therapeutic nucleic acid, peptide or protein. The purpose of creating the vectors in Rosenberg reference was to deliver them for therapy, and Rosenberg teaches a gene therapy vector, this implies an in vivo delivery (see abstract, claims 1 and 8). Therefore, combined references are unpatentable over the instant claims. In regards to Applicant's arguments that "7,144,869 was filed after the publication of US 2002/0064520", the U.S. patent 7,144,869 claims priority to earlier applications and patents (for example, Dec 13, 1995). US 2002/0064520 was published

May 30, 2002. Since U.S. patent 7,144,869 teaches the method of delivering a polynucleotide to a primate liver cell, and US 2002/0064520 teaches delivery of vectors that include therapeutic nucleic acid, peptide or protein as gene therapy vector, it would have been obvious for one of ordinary skill in the art to deliver the protein or peptide directly to the target tissue. Both U.S. patent 7,144,869 and US 2002/0064520 were filed before the instant application, both prior arts can be used as prior arts.

Conclusion

25. No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to JULIE HA whose telephone number is (571)272-5982. The examiner can normally be reached on Mon-Thurs, 5:30 AM to 4:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Anish Gupta/
Primary Examiner, Art Unit 1654

/J. H./
Examiner, Art Unit 1654